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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,516	06/08/2000	CHRISTOPHER ROBERT BEBBINGTON	078883/0119	3014

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/24/2002 23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/508,516	Applicant(s) BEBBINGTON ET AL.	
	Examiner Michael Wilson	Art Unit 1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21-24,30 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21-24,30 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Art Unit of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-3-02, paper number 21, has been entered.

Applicant's arguments filed 4-3-02, paper number 22, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The amendment filed 1-2-02, paper number 18 was not entered in favor of the amendment filed 4-3-02, paper number 22. The amendment filed 4-3-02 has been entered. Claims 20, 25, 26, 28, 29, 31-41 and 43-45 have been canceled. Thus, claims 1-19, 21-24, 30 and 42 are pending and under consideration in the instant office action.

Claim Objections

The clean copy of the claims (pg 1-4 of applicants response) should not have "(Twice amended)".

Dependent claims 2-23 and 42 should begin "The...."

The phrase "a retroviral" in claim 24 should be "the retroviral."

The semicolon in claim 1(b), line 1, should be a comma.

The semicolons in claim 1(b)(iii)(b), line 1 and 3, should be a comma.

The semicolons in claims 2-4, 8 and 12 should be commas.

The quotation marks in claim 1 should be deleted.

Claim Rejections - 35 USC § 112

1. Claims 1-19, 21-24, 30 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The combination of elements in the vector of claim 1 cannot be found in the specification as originally filed. Specifically, the splice donor site within the 5' LTR of the vector and the splice donor site "at" the 3' U3-R region of the pro-vector cannot be found. Nor can support be found for translocation of the splice donor site from the 3' U3-R to the 5' LTR be found. The addition

of the elements in claims 2-24, 30 and 42 to the vector of claim 1 cannot be found in the specification as originally filed. Therefore, claims 1-24, 30 and 42 are new matter.

2. Claims 1-19, 21-24, 30 and 42 remain rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for the selective expression of the hygromycin - neomycin gene pair or the hygromycin-p450 gene pair does not reasonably provide enablement for any nucleotide sequence of interest (NOI) as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record.

Applicants argue that one of skill would be able to compensate for cryptic splice sites by identifying and altering the sites as taught by Sebillon (1995), Maruyama (1995) and Burns (1995). Applicants argument is not persuasive because it was unpredictable whether a gene contained a cryptic splice site. Therefore, it was unpredictable what gene to put into the vector claimed such that proper translocation and protein expression could be obtained. The specification does not overcome the unpredictability in the art by teaching how to make and/or use the vector claimed encoding any gene of interest having a cryptic splice site for reasons of record.

The specification does not enable making a retroviral vector by mere reverse transcription as claimed. The translocation of the splice donor site upstream of the splice acceptor site is a result of reverse transcription which is not clearly set forth in the claims. Integration into the host cell's genome of the pro-virus results in addition of a functional intron which contains a

nucleotide sequence of interest (NOI). Claim 1 does not require the intron has an NOI or that integration of the provirus into the cell genome results in addition of the functional intron. Since the gene of interest is within the intron, no protein from the gene will be expressed due to splicing out of the sequence; however, the claims 4 and 13 require expression of the NOI. Further, expression of a second gene of interest downstream of the splice acceptor site is activated because of the functioning intron. However, claim 1 does not require a second NOI. These elements are essential to the invention. The first NOI has no function if there is no second NOI. The first NOI does not function unless it is within an intron. The method of making the vector and translocation cannot be performed merely by reverse transcription as claimed. The essential elements describing the structure and function of the vector and pro-vector are not in the claims. The steps required to make the vector using the pro-vector are not in the claims.

Claim 5 recites the vector is capable of providing a therapeutic or diagnostic effect. The specification does not enable transfecting cells within a host or using the vector claimed for diagnosis or therapy for reasons of record. Applicants argue claim 5 has been amended so that it no longer recites a "therapeutic agent"; therefore, applicants argue the rejection is moot. Applicants argument is not persuasive because a nucleic acid sequence or product thereof that has a therapeutic effect is a therapeutic agent. The specification does not enable using a vector comprising a nucleic acid sequence "capable of providing a therapeutic or diagnostic effect" to obtain a therapeutic or diagnostic effect for reasons of record.

3. Claims 1-19, 21-24, 30 and 42 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 1 remains indefinite for reasons of record because it is unclear how the "retroviral vector comprising..." correlates to the "retroviral pro-vector" or how the retroviral vector is made.

In general, the description of "a first nucleotide sequence ("NS") containing a functional splice donor site" is wordy and can be adequately described as "a functional splice donor site." The same is true for the "second" NS.

The description of a splice donor in the retroviral vector and a splice donor in the retroviral pro-vector in claim 1 is confusing because the claim does not clearly set forth that the splice donor in the retroviral vector is the same splice donor in the retroviral pro-vector. The same is true for the splice acceptor.

The method of making the retroviral vector as set forth in claim 1 (iii) is unclear because it does not clearly set forth the method steps required to make the retroviral vector. The phrase "the retroviral vector is formed as a result of reverse transcription of a retroviral pro-vector..." (claim 1, step (iii), line 1 and line 6-7) does not clearly set forth the method steps required to make the retroviral vector. Repeating the phrase does not further limit the claim or describe the method steps required to form the retroviral vector.

It is unclear if "the retroviral vector comprising the first... ...acceptor site" is the retroviral vector in (iii), line 1, or a different retroviral vector. Use of the phrase "comprising the first... ...acceptor site" (iii), line 4-5) is confusing and does not further limit the retroviral vector.

The phrase "a copy of the first NS containing the splice donor site at the 3' U3-R region of the retroviral provector is translocated to the 5' LTR of the retroviral vector" is indefinite. First, "a copy of the first NS containing the splice donor site at the 3' U3-R region of the retroviral pro-vector" should be written more succinctly. Second, it is unclear how the "reverse transcription" correlates to the "translocation." Does translocation occur before, after or during reverse transcription? Third, the claim does not clearly set forth the step of "translocation." Translocation means to transfer to a new position. It is unclear if the copy is moved to a new position in the same vector or if it is moved to a new position in a different vector. Is the copy inserted into the 5' LTR of the retroviral pro-vector, thereby forming the retroviral vector or is the copy inserted into directly into the 5' LTR of the retroviral vector?

It is unclear how a retroviral vector comprising an NOI (claim 1, i) can be made when the retroviral pro-vector does not comprise the NOI and the method used to make the retroviral vector does not require the NOI.

Therefore, claim 1 as a whole is indefinite.

Claims 1 and 2 as newly amended are indefinite because it is unclear whether "containing" is open language similar to "comprising" or if "containing" is closed language, similar to "consisting of."

The phrase "the 5' long terminal repeat" in claim 1 lacks antecedent basis because the vector may not have an LTR.

The phrase "the 3' U3-R region" in claim 1 lacks antecedent basis because the vector may not have a 3' U3-R region.

The phrase "at the 3' U3-R region" in claim 1 is unclear because the metes and bounds of when a nucleic acid sequence is "at" the 3' U3-R region cannot be determined. Must the nucleic acid sequence be directly adjacent to, nearby or within the 3' U3-R region?

The term "flank" in claim 1 is indefinite. Flank means "to one side" (see http://dictionary.cambridge.org; enter "flank"). It is unclear if the claims are intended to encompass having both the splice acceptor and splice donor upstream of the NOI or if the splice acceptor must be downstream of the NOI.

The metes and bounds of what applicants consider a "non-functional donor splice site" (claim 2) is indefinite. It is unclear whether any nucleic acid sequence that does not function as a donor splice site is encompassed by the claim or if the nucleic acid sequence has a particular structure or function. As such the metes and bounds of nucleic acid sequences encompassed by the phrase cannot be determined.

It is unclear how claim 4 further limits claim 3 because the pro-vector must comprise the second NOI for the retroviral vector to comprising the second NOI.

Claim 4 is indefinite because the pro-virus of claim 1 does not comprise a first NOI; therefore, it cannot comprise a "second NOI".

Claim 5 is indefinite because a nucleic acid does not provide a therapeutic or diagnostic effect - a protein provides a therapeutic or diagnostic effect. However, the claim does not require the NOI encodes a protein.

Claim 6 is indefinite because a nucleic acid does not provide selectability - a protein provides selectability. However, the claim does not require the NOI encodes a protein.

Claim 6 is indefinite because it is unclear what applicants consider "essential elements" of a virus.

Claim 6 is indefinite because it is unclear if "a part thereof" refers to the viral element or both the viral element and the agent. As such , it is unclear to what "combination thereof" refers.

Claim 6 is indefinite because "is or comprises" is confusing.

Claim 7 is indefinite because it is unclear when a nucleic acid sequence is "at" the 3' end of a retroviral pro-vector for reasons cited above regarding "at" in claim 1, step (iii).

Claim 7 is indefinite because it is unclear if "the first NS" refers to the first NS of the retroviral vector or the first NS of the pro-vector.

Claim 7 is indefinite because it is unclear when a nucleic acid is "near" the 3' end of a retroviral pro-vector. How near is near?

Claim 7 is indefinite because it is unclear whether the "retroviral pro-vector" is the pro-vector of claim 1 or a different vector.

Claim 8 is indefinite because it is unclear if "a part thereof" refers to the coding sequence or both the control element and the coding sequence .

Claims 9 and 10 are indefinite because it is unclear if "the first NS" refers to the first NS of the retroviral vector or the first NS of the pro-vector.

Claim 12 is indefinite because it is unclear if "the second NS" refers to the second NS of the retroviral vector or the second NS of the pro-vector. As such, it cannot be determined where the packaging signal is located.

Claim 12 is indefinite because it is unclear how the phrase "such that splicing is prevented at a primary target site" correlates to claim 1. It is unclear how the phrase further limits the structure or function of the vectors because splicing is not require in the method and because the retroviral vector or pro-vector do not have "target sites."

Claim 12 is indefinite because the metes and bounds of "primary" target sites cannot be determined. When is a target site "primary?"

Claim 13 is indefinite because it is unclear if "the second NS" refers to the second NS of the retroviral vector or the second NS of the pro-vector.

Claim 13 is indefinite because it is unclear how the phrase "such that the first NOI is expressed at a primary target site" correlates to claim 1. It is unclear how the phrase further limits the structure or function of the vectors because expression is not require in the method and because the retroviral vector or pro-vector do not have "target sites."

Claim 13 is indefinite because the metes and bounds of "primary" target sites cannot be determined. When is a target site "primary?"

Claim 14 is indefinite because it is unclear if "the second NS" refers to the second NS of the retroviral vector or the second NS of the pro-vector.

Claim 14 is indefinite because it is unclear whether the "one or more additional NOIs" encompasses the NOI in claim 1 (i) or only additional NOIs.

The metes and bounds of where and how a second NS can be inserted "such that additional NOIs may be inserted" cannot be determined (claim 14).

Claim 15 is indefinite because nucleic acid sequences cannot encode any "immunological molecule." Immunological molecules encompass non-proteins; however, nucleic acid sequences can only encode proteins.

Claims 15-17 are indefinite because it is unclear how the second NS can comprise both a splice acceptor and encode an immunological protein.

The word "additionally" in claim 18 is confusing because the vector of claim 1 does not have an intron. The phrase "further comprises..." or deletion of "additionally" is preferred.

Claim 19 is indefinite because positions of the intron that "restrict expression of an NOI in a target site" cannot be determined. Therefore, the position of the intron is unclear.

Claim 19 is indefinite because it is unclear how the phrase "so that it restricts expression of at least one of the NOIs in a desired target site" correlates to claim 1. It is unclear how the phrase further limits the structure or function of the vectors because expression is not require in the method and because the retroviral vector or pro-vector do not have "target sites."

The term "NOIs" in claim 19 lacks antecedent basis because claim 1 only has one NOI.

Claim 19 is indefinite because the metes and bounds of "desired" target sites cannot be determined. When is a target site "desired?"

The phrase "wherein the vector or pro-vector is a murine oncoretrovirus or a lentivirus retroviral vector or pro-vector" is confusing (claim 21). As written, the vector (1st occurrence) may be a pro-vector (second occurrence) which does not make sense. The pro-vector (1st occurrence) may be a pro-vector (second occurrence) which does not further limit the pro-vector. As written, "pro-vector" (second occurrence) does not further limit the "vector or pro-vector" (1st occurrence).

Claim 22 is indefinite because it is unclear "the vector" refers to only the "vector" in claim 21 or both the vector and the pro-vector. It is unclear if the viruses listed are intended to further limit the "lentivirus", the "retrovirus", the "oncoretrovirus," or the "vector" in claim 21.

Claim 23 is indefinite because the distinction between a "pro-vector" in claim 1 and "provirus" in claim 23 cannot be determined.

Claim 23 is indefinite because a vector is not a provirus.

Claim 23 is indefinite because the method portion of claim 1 does not require integration and the phrase "integrated provirus" does not alter the structure or function of the vector.

Claim 30 is indefinite because it does not further limit the pro-vector of claim 1 and does not set forth the structure or function of the pro-vector.

Claim 42 is indefinite because the metes and bounds of when or how a vector "differentially expresses" an NOI cannot be determined.

Claim 42 is indefinite because NOIs lacks antecedent basis. The vector of claim 1 only has one NOI.

Claim 42 is indefinite because claim 1 does not require expression of an NOI or transduction of target cells. Therefore, it is unclear how the phrase further limits the vector claimed or how the structure or function of the vector is altered.

Claim Rejections - 35 USC § 102

The rejection of claims 1-6, 9, 10, 12-14, 18-24 under 35 USC 102(b) as being anticipated by Morgenstern (Morgenstern et al., 1990, Nucleic Acids Research 18(12):3587-96) is withdrawn because Morgenstern taught the splice donor was next to the 5' UTR and not within the 5' UTR as claimed.

The rejection of claims 1 and 15-17 under 35 USC 102(b) as being anticipated by Takeda (Takeda et al., 1985, Nature, Vol. 314, 452-454) is withdrawn because Takeda did not teach the splice donor was in the 5' LTR.

The rejection of claims 1 and 9-11 under 35 USC 102(b) as being anticipated by Kriegler (Kriegler et al., 1984, Cell, Vol. 38, pages 483-491) is withdrawn because Kriegler did not teach the splice donor was in the 5' LTR.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

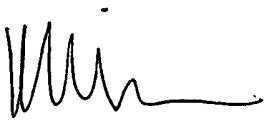
Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL C. WILSON
PATENT EXAMINER

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1. To border; to touch. *Bp. Butler.*

2. To be posted on the side.